IMPACT OF DORSOLATERAL PERIAQUEDUCTAL GRAY LESIONS ON SHOCK-INDUCED HYPERALGESIA

A Senior Thesis

By

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ABSTRACT

Prior exposure to shock lowers vocalization thresholds to heat and facilitates the acquisition of conditioned fear when training is conducted in a different context. These observations have been taken as evidence that shock exposure increases the affective impact of subsequent aversive stimuli, a phenomenon known as hyperalgesia. The present study explores whether this hyperalgesia depends on neurons within the dorsolateral periaqueductal gray (dlPAG). Experiment 1 showed that lesioning either the rostral or caudal dlPAG prevented the shock-induced reduction in vocalization thresholds. Experiment 2 showed that lesioned subjects also failed to exhibit facilitated learning after shock exposure. Taken together, these results suggest that the dlPAG plays a critical role in the production of shock-induced hyperalgesia.

INTRODUCTION

Understanding the experience of pain has eluded both scientists and philosophers alike for many years. What is pain, or perhaps more importantly, why bother to study such a subjective phenomenon? In most cases, pain is thought to be an adaptive mechanism that motivates humans and animals to avoid tissue damage and promotes recuperation after damage has occurred. There are some instances, however, in which pain has seemingly no adaptive value (e.g., migraine headaches, menstrual cramps, spinal cord injury, etc.) and instead produces needless suffering. It is cases like these that motivate our research and drive us to study pain and its underlying mechanisms.

Much research in the pain literature has revealed a tremendous variability in our perception of pain. In some circumstances, a single noxious stimulus may lessen pain sensitivity (hypoalgesia) in some instances while enhancing pain (hyperalgesia) in others. My study explores the neural mechanisms that underlie the latter phenomenon. Recent evidence indicates that exposure to a noxious event, per se, often induces hyperalgesia. Depending on the neural system engaged, this hyperalgesia can last minutes, to days, to weeks (Coderre, Katz, Vaccarino, & Melzack, 1993). The particular mechanism engaged appears to depend on the severity of the noxious event; severe tissue damage sensitizes spinal neurons whereas milder stimuli enhance pain through supraspinal systems (King, Crown, Sieve, Joynes, Grau, & Meagher, submitted). In support of this evidence, Grau and his colleagues have shown that exposure to 3, 1-mA tail shocks lowers vocalization thresholds to both radiant heat and subsequent shock (Illich, King, & Grau, 1995; King, Joynes, Meagher, & Grau, 1996). If prior shock exposure increases the

affective impact of noxious stimuli, it should also enhance their ability to reinforce learning. Supporting this, they showed that previously shocked rats exhibit greater fear conditioning (measured by freezing) when given a weak shock in a different context (King et al., 1996). Taken together, these results suggest that prior exposure to shock enhances the affective impact of subsequent aversive stimuli.

Interestingly, at the same time that hyperalgesia is observed, protective reflexes (e.g., paw and tail withdrawal from radiant heat) are inhibited (antinociception). Unlike hyperalgesia, which appears to reflect an unconditioned response that generally enhances pain reactivity, the antinociception observed after shock has a more selective impact (only inhibiting reactivity to stimuli applied to the distal region of the tail or paw [Prentice, Joynes, Meagher, & Grau, 1996]) and depends on both associative and memorial processes (Grau, 1987a; Fanselow, 1986).

While a great deal is known about the neural systems involved in antinociception, very little is currently known about the supraspinal mechanisms involved in shock-induced hyperalgesia. We do know from prior research that the effect is eliminated by both decerebrations and lesions of the frontal pole (King et al., submitted). Also, rats made unconcious with pentobarbital do not exhibit shock-induced hyperalgesia (King, et al., submitted). Together these results suggest that the effect depends on higher brain systems. We know virtually nothing, however, about the specific neural systems involved.

One region of interest is a structure in the brainstem known as the periaqueductal gray (PAG). Dozens of studies suggest that the dorsolateral and lateral regions of the periaqueductal gray (as others have done [e.g., Fanselow, DeCola, & Young, 1993] we will refer to this region as the dlPAG) play a critical role

in integrating motivational, affective, and sensory inputs, organizing escape responses and generating vocalizations (Bandler & Shipley, 1994; Behbehani, 1995; Carrive, 1993; Depaulis, Bandler, & Vergnes, 1989; Holstege, 1991; Jurgens, 1994). Interestingly, these behaviors appear to vary along the rostral-caudal pole (Bandler & Depaulis, 1991). Stimulation of the rostral region leads to a backward defense, or a rearward movement, and sonic vocalizations characteristic of threat responses. In contrast, stimulation of the caudal dlPAG produces a flight response of forward avoidance and ultrasonic vocalizations. Given its role in defense, anxiety, and vocalization, I hypothesized that the dlPAG may play a critical role in shock-induced hyperalgesia.

In the present experiments, I examined this hypothesis by assessing the impact of neurochemical lesions of the rostral and caudal dlPAG on shock-induced sensitization of pain as measured by reactivity to radiant heat (Experiment 1) and conditioned freezing (Experiment 2).

GENERAL METHODS

Subjects. The subjects were 102 male albino Sprague-Dawley rats obtained from Harlan (Houston, TX). They were 94-108 days old at the time of surgery and weighed between 350 and 425 g. Animals were individually housed and maintained on a 12-hr light-dark cycle. Food and water were available ad libitum.

Apparatus. Restraining tubes were constructed from Plexiglas to be 22.0 cm in length and 6.8 cm in diameter with a Plexiglas sheet closing the front of each tube. A 5.5 cm wide floor lying 5.3 cm from the top of the tube was also constructed from Plexiglas. A strip in the middle of the floor (1.3 cm in width) extended 4.8 cm beyond the open end of each tube. Tubes were painted black to block external light, and

ventilation holes were drilled through their tops. Tubes were routinely cleaned between subjects. Chamber fans provided a background noise level of approximately 60 dB.

Constant current tail shock (60-Hz AC, 1-mA) was generated from the same 660-V transformers used in earlier studies (e.g., Grau, 1987a, 1987b; Illich et al., 1995) and was administered through electrodes constructed from a modified fuse clip. Electrodes were covered with electrode paste, positioned approximately 7 cm from the tip of the tail, and secured in place with Orthaletic porous tape.

Vocalization during shock was measured with a small microphone (Radio Shack 270-092B) positioned behind a 9.4 mm hole that was drilled through the closed end of the tube, 3.5 cm from the bottom. A Sanyo amplifier (DCA 611) selectively amplified frequencies above 1500 Hz. At 80dB, frequencies below 1500 Hz were attenuated by approximately 8 dB. The response function was relatively flat ($\pm$ 0.5 dB) from 1500 to 20000 Hz. A full-wave rectifier receiving output from the amplifier provided a direct-current (DC) voltage that was proportional to the sound intensity recorded by the microphone. This voltage was then transferred to a Macintosh computer by way of an analog-to-digital (A-D) converter (Alpha Products, Analog 80). The computer read and recorded the digital input approximately 25 times per second. A 4000-Hz sine-wave tone was then used to calibrate the system by determining the relation between the digital input and the loudness of the tone. Based on this derived function, the digital inputs were converted to decibels (dB). A lower cutoff of 78 dB was introduced to prevent extraneous sounds, such as breathing, from contaminating the data. Equipment capabilities allowed for an upper cutoff of 125 dB.

In Experiment 2, testing occurred in Model RTC-021 (BRS/LVE) chambers that were 26.8 cm high, 26.0 cm wide, and 30.5 cm long. Side walls were made of aluminum, while ceiling, front, and rear walls were constructed from clear Plexiglas. A grid floor was formed from stainless steel rods (0.4 cm in diameter) spaced 1.5 cm apart. A 660-V transformer was used in combination with a shock scrambler to administer a constant current, 0.3-mA shock through the rods. A background noise of approximately 60 dB was generated by chamber fans. In order to distinguish contexts, the tubes and observation chambers were situated in separate rooms and were cleaned with different solutions (20% vinegar or 1% ammonia) between subjects.

Surgery. Subjects were anesthetized with 50 mg/kg pentobarbital, and lesions were performed in the same manner as described in Fendt et al. (1994). To lesion the rostral PAG, two sets of bilateral lesions were made at the following coordinates (Paxinos & Watson, 1986): 1) 5.6 mm posterior from Bregma, ±0.4 mm lateral from the midline, and 6.0 mm ventral from the surface of the skull; and 2) 6.6 mm posterior from Bregma, ±0.6 mm lateral, and 6.0 mm ventral. Caudal lesions were made bilaterally at coordinates: 1) 7.7 mm posterior from Bregma, ±0.8 mm lateral, and 5.7 mm ventral; and 2) 8.7 mm posterior from Bregma, ±1.0 mm lateral, and 5.7 mm ventral. The lesions were made using a 0.2 M solution of quinolinic acid (Sigma) dissolved in 0.1 M PBS and adjusted to pH 7.6 with NaOH. At each site, 0.3 µl of the solution was injected using a Hamilton 1.0 µl syringe. The solution was infused at a rate of 0.05 µl/30s, and the syringe was left in place for 3 minutes after the injection was made. Control subjects received injections of the vehicle alone. Half of the sham operated subjects received vehicle injections at the rostral coordinates, while the

remaining half received injections at the caudal coordinates. All subjects were allowed to recover for 2 weeks following surgery with ad lib access to food and water.

Behavioral Measures. Tail-flick and vocalization thresholds to heat in Experiment 1 were measured using an automated tail-flick device. Heat was provided by a 375-W movie light that was focused on the rat's tail by means of a condenser lens positioned 8.0 cm below the light source. The light source illuminated approximately 2.0 cm of the rat's tail, and its intensity was controlled by an AC potentiometer (Leviton, #6681-W).

The rat's tail rested in a 0.5 cm deep groove that was cut into an aluminum block positioned 4.7 cm below the condenser lens. Plastic barricades (6 cm x 6.7 cm) were placed along the side edges of the aluminum block to keep the rat's tail under the heat source. A photocell located under the groove was used to automatically detect when the rat moved its tail laterally by at least 0.5 cm. Vocalization was detected using the microphone described above. A computer monitored both the circuit controlled by the photocell and the intensity output from the microphone and recorded the latency for each response. A 10 cm wire hook that was covered with heat shrink tubing was attached to the end of the tail. The hook was placed over an elastic band located 11 cm away from the block. The flexibility of the elastic band allowed for a tail-flick response that would expose the photocell, but continue to hold the rat's tail under the heat source until a vocalization was also recorded. After both responses were detected, the heat was terminated. A cutoff latency of 8-s was used to prevent tissue damage. The duration of the trial was timed to the nearest 0.01s. False alarm trials during which no heat was presented were also included either 30 sec before or after

each test stimulus to ensure that results were not due to an overall increase in responding.

In Experiment 2, the rats' behavior in the test chamber was scored as freezing or activity. Freezing was defined as the absence of all visible movement of the body except for movement necessary for respiration. All other behaviors were scored as activity. (For further description, see Fanselow, 1984.) On the first test day, the experimenter rating the rat's behavior was unaware of whether the rat had previously received tail shock in the restraining tubes. On the second test day, the experimenter was unaware of whether the rat had received shock in either the tube or the observation chamber.

Histology. After testing was complete, subjects received a lethal dose of pentobarbital and were perfused intracardially with 0.9% saline followed by 10% buffered formalin. The brains were then removed and stored in 10% formalin for at least 1 week. Frozen sections (50 μm) through the lesion were then made and Nissel stained. The extent and location of cell loss was determined by microscopic analysis and transcribed onto atlas sections from Paxinos & Watson (1986). All histological analyses were performed by an experimenter who was blind to the subjects' results and test conditions.

The extent and location of representative rostral (top) and caudal (bottom) dlPAG lesions are depicted in Figure 1. Quinolinic acid induced damage of brain tissue as indicated by marked gliosis. In some cases, cell damage extended into areas just dorsal or just lateral to the target region, including parts of the adjacent deep layers of the superior colliculus. Rats with either unilateral lesions or poorly localized lesions (e.g., those that included damage to the ventolateral PAG) were

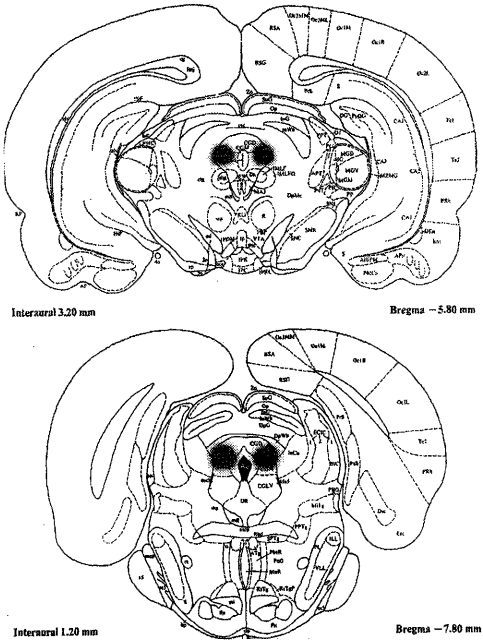

Figure1. Representative lesions of the rostral (top) and caudal (bottom) portions of the dorsolateral periaqueductal gray (dlPAG).

excluded from the study. In Experiment 1, six rats receiving rostral lesions and four rats receiving caudal lesions were not included in the final analysis because they had either unilateral lesions or lesions in some region other than the dlPAG. In Experiment 2, five rostral-lesioned and three caudal-lesioned rats were excluded.

Statistics. In both experiments, the results were analyzed using analysis of variance (ANOVA) and were considered significant if $p < .05$. All post hoc comparisons were made using the Bonferroni t-test.

EXPERIMENT 1

The present experiment looked at the impact of dlPAG lesions on shock-induced hyperalgesia as measured by vocalization latencies to radiant heat. To examine whether the lesions affected antinociception, tail withdrawal latencies were also assessed. Due to the behavioral differences observed during stimulation of either rostral or caudal portions of the dlPAG, both lesion sites were included as separate test conditions.

Procedure

Excluding animals rejected on the basis of histological analysis, 16 rats served in each surgery condition: rostral-lesioned, caudal-lesioned, and sham (8 sham rostral & 8 sham caudal). At the end of the surgical recovery period, subjects were put into the restraining tubes, hooks were attached to the tip of their tails, and they were allowed to acclimate for 15 min. Baseline tail-flick and vocalization latencies were measured. Shock electrodes were then taped to their tails, approximately 12cm from the tip, and half of the rats in each surgery condition received 3, 0.75-s 1 mA shocks. The remaining rats were restrained for an equivalent amount of time but received no

shock. Tail withdrawal and vocalization latencies to heat were measured 2 and 8 min later.

Results

Both rostral and caudal dlPAG lesions eliminated the hyperalgesia observed when vocalization thresholds were assessed, but had no effect on the magnitude of antinociception observed when tail withdrawal latencies were measured.

Shams. An ANOVA revealed that the baseline tail withdrawal and vocalization latencies for sham rostral and sham caudal dlPAG lesions did not differ, all $\underline{F}$s < 0.5, $\underline{p}$ > .05. Since there were also no differences in tail-flick or vocalization latencies between the two sham groups after shock, all $\underline{F}$s < 1.20, $\underline{p}$ > .05, the data were collapsed across the two sham groups.

False Alarms. None of the subjects tail-flicked and only three subjects vocalized during the false alarm trials. Two of these rats vocalized during pre-shock period (1 rat from the shocked-sham group and 1 rat from the shocked-rostral group), while the third (from the unshocked-caudal group) vocalized during a post-shock trial. Mean vocalization latencies ranged from 7.24 ± .76 to 8.00 seconds. Separate ANOVAs revealed that lesion site did not significantly affect false alarms for any of the measures, all $\underline{F}$s < 1.00, $\underline{p}$ > .05.

Tail Withdrawal Latencies. All subjects exhibited similar baseline thresholds prior to shock. Baseline means (±SEM) ranged from 4.51 (± .45) s to 5.15 (± .71) s. An ANOVA confirmed that the baseline scores did not differ, all $\underline{F}$s < 0.28, $\underline{p}$ > .05.

The tail withdrawal latencies observed after shock treatment are depicted in the top panel of Figure 2. Neither rostral nor caudal lesions disrupted the shock-induced increase in latency to respond. An ANOVA revealed that the main effect of

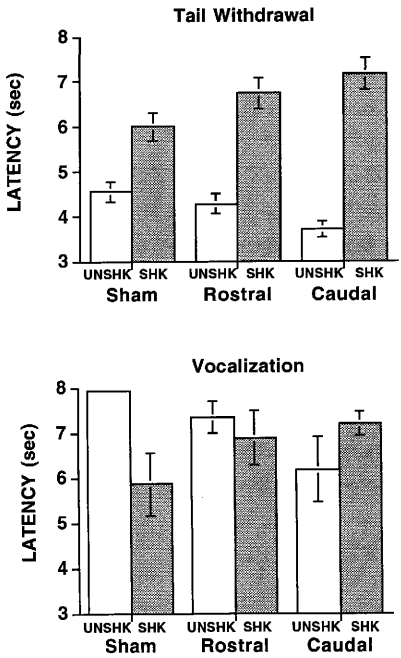

Figure 2. Tail withdrawal (top) and vocalization (bottom) latencies to radiant heat for subjects in each of the three surgery conditions. Rats that previously received shock (SHK) are represented by filled bars while rats that received no shock (UNSHK) are represented by unfilled bars. Error bars indicate standard error (*SE*).

shock was statistically significant, F (1,42) = 35.21, p >.05. Neither the main effect of lesion nor the shock X lesion interaction was significant, both Fs < 1.99, p > .05, indicating that shock increased tail withdrawal latencies irrespective of whether animals had received lesions.

Vocalization Latencies. All subjects exhibited similar baseline vocalization thresholds to shock. Baseline means (±SEM) ranged from 6.61 (± .69) s to 7.86 (± .14). An ANOVA confirmed that baselines did not differ, all Fs < 0.07 , p > .05.

The vocalization thresholds observed after shock are depicted in the bottom panel of Figure 2. Shock exposure reduced vocalization thresholds in sham operated, but not lesioned subjects. Both rostral and caudal lesions eliminated the shock-induced decrease in vocalization latency. An ANOVA revealed that neither the main effect of lesion nor shock was significant, both Fs < 1.47, p > .05. The lesion X shock interaction, however, was statistically significant, F (2,42) = 19.23, p < .05. To further explore the nature of this interaction, I assessed the impact of shock for each lesion condition using the Bonferroni t-test. These comparisons revealed that shocked rats in the sham condition exhibited significantly lower thresholds than sham rats that were unshocked, t = 4.80, p < .01. No other differences were significant, both ts < 2.38, p > .05.

EXPERIMENT 2

The results indicate that both rostral and caudal dlPAG lesions eliminate the shock-induced hyperalgesia as measured by a decrease in vocalization thresholds to radiant heat. Experiment 2 examined whether these lesions affect another measure of hyperalgesia -- the shock-induced facilitation of fear conditioning.

Procedure

Excluding animals rejected on the basis of histological analysis, 12 rats served in each surgery condition: rostral-lesioned, caudal-lesioned, and sham (6 sham rostral & 6 sham caudal). The tubes were cleaned with the appropriate solution (counterbalanced across test conditions), the rats were placed into restraining tubes, and the electrodes were attached to their tails. After a 15 min acclimation period, half the rats in each surgery condition received either three 1-mA, 0.75-s shocks at 20-s intervals or an equivalent period of restraint with no shock. The rats were then moved to the observation chamber, which had been cleaned with the other solution, and their baseline freezing levels were assessed for 3 min at 3-s intervals. All rats then received a 0.3-mA, 0.5-s test shock. Immediately following the shock, freezing levels were measured for another 2 min after which the rats were returned to their home cages. Twenty-four hr later, rats were again placed in the observation chambers and their freezing levels were recorded for 8 min.

Results

As in past studies, prior shock exposure facilitated fear conditioning in sham operated subjects. This effect was blocked by both rostral and caudal dlPAG lesions.

Shams. An ANOVA revealed that freezing levels for sham rostral and sham caudal lesions did not differ on either test day, all $\underline{F}$s < 1.0, $\underline{p} > .05$. Given this, I collapsed the data across the two sham conditions.

Freezing on Day 1. Prior to the application of the weak foot shock in the observation chambers, the mean levels of freezing ranged from 0.3 ± 0.3 to 4.2 ± 2.9% of the total time measured. These differences did not approach statistical significance, all $\underline{F}$s < 2.53, $\underline{p} > .05$.

The amount of freezing observed immediately after foot shock in the chamber is depicted on the left side of Figure 3. Previous exposure to shock had an obvious impact on overall freezing levels. An ANOVA confirmed that the main effect of prior shock treatment was significant, F (1, 30) = 8.091, $p < .01$. Although lesions appear to reduce freezing for rats in the shocked condition, neither the main effect of lesion nor the shock X lesion interaction was significant, both Fs < 2.10, $p > .05$.

Freezing on Day 2. The levels of freezing observed on Day 2 are depicted on the right side of Figure 3. The 8 min observation period was divided into four 2 min bins so that freezing levels could be examined over time. The results indicate that both rostral and caudal dlPAG lesions eliminate shock-induced enhancement of conditioned freezing and that this effect increases over time. Neither the main effects of shock nor lesion, nor the shock X lesion interaction was significant, all Fs < 3.09, $p > .05$. However, when effects were considered over time, significant results were found for the shock history X lesion X time interaction, $F = 2.21$, $p < .05$. Post hoc comparisons of shocked and unshocked groups at each time point revealed that shocked rats in the sham condition showed significantly higher levels of freezing 4 to 8 min following reexposure to the test context, all ts > 4.80, $p < .05$. No other differences were significant, all ts< 1.78, $p > .05$.

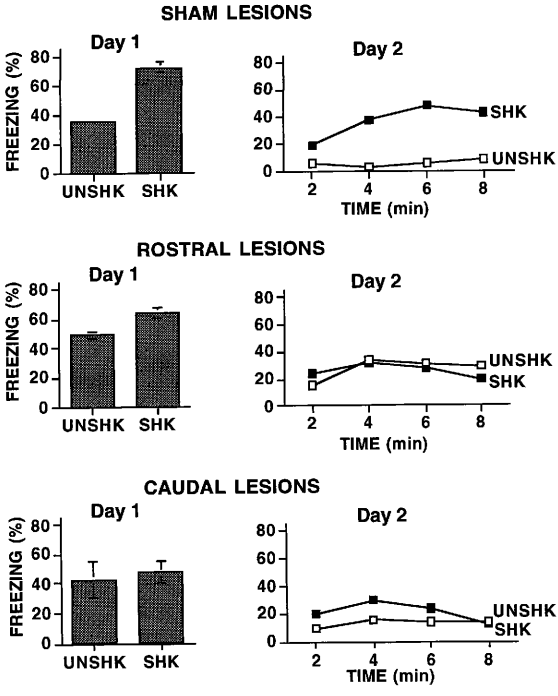

Figure 3. The percentages of freezing observed following shock exposure on Day 1 (left) and when the rats were reexposed to the context on Day 2 (right) for each surgery condition. All rats received either 3 brief tail shocks (SHK) or no shock (UNSHK) in the restraining tubes prior to testing. Error bars indicate standard error (*SE*).

GENERAL DISCUSSION

The present experiments were designed to elucidate the neural mechanisms that underlie shock-induced hyperalgesia by examining the role of the dorsolateral column of the PAG in this effect. As in past studies, sham operated rats exhibited lower vocalization thresholds to radiant heat and demonstrated facilitated learning after exposure to shock. Both of these effects were eliminated in rats with dlPAG lesions, supporting my hypothesis that this region is important in hyperalgesia. In contrast, lesions had virtually no effect on shock-induced antinociception, evidence that the two phenomena depend largely on separate neural systems.

In general, these findings fit well with the presumed role of the dlPAG in the organization of defensive behavior (e.g., Bandler & Depaulis, 1991; Bandler & Shipley, 1994; Behbehani, 1995; Carrive, 1993; Depaulis, Bandler, & Vergnes, 1989). For example, Fanselow (1994) suggests that an animal's mode of defensive responding varies according to its level of fear. Low levels of fear activate pre-encounter defenses (e.g., meal-pattern reorganization); moderate levels promote post-encounter defenses, such as freezing; and extremely high levels of fear (e.g., following physical contact with a predator) elicit active defenses often referred to as the circa-strike mode. This later defense mode is of most relevance to the present study because of its reliance on the dlPAG. From this perspective, enhanced vocalization and nociceptive reactivity could be viewed as components of the circa-strike mode. What is novel is that my data suggest these defensive reactions to aversive stimuli may be sensitized because the dlPAG increases the affective impact.

Past studies suggest that the antinociception observed 2 min after mild shock is nonopiod in form (Grau, 1984) and depends on the dlPAG (Fanselow, 1994). Yet,

dlPAG lesions had no impact on the magnitude of antinociception observed 2 min after shock. However, other studies (Grau 1984, 1987b) suggest that manipulations designed to selectively attenuate the nonopiod component do not alter the magnitude of the antinociception, but rather change the form of the antinociception from nalterxone-insensitve (nonopiod) to naltrexone-reversible (opiod). Thus, in explanation of my data, lesions may well have diminished the nonopiod antinociception in part, but the effect may have been masked by the presence of opiod-mediated antinociception. Further studies involving opiod antagonists (e.g., naltrexone) would be needed to make this determination.

Also unexpected was the fact that both rostral- and caudal-lesioned animals were able to vocalize in response to the test stimuli despite the putative role of the dlPAG in the regulation of vocal behavior (e.g., Jurgens, 1991, 1994; Larson, 1991). Results from Experiment 1 clearly indicate that neither rostral or caudal lesions affected subjects' latency to vocalize to radiant heat. Understanding the implications of these results, however, requires an appreciation of the simplicity of my vocalization measure. By measuring thresholds, all discriminating information (i.e., intensity, frequency, etc.) becomes irrelevant, and any cry greater than 89 dB is considered a response. It is important to note that while the entire dorsolateral column of the PAG is involved in vocal behavior, the type of vocalization elicited varies as a function of region stimulated, where rostral stimulation leads to sonic vocalization while caudal stimulation leads to ultrasonic cries (Davis & Zhang, 1991). It may be the case that under normal conditions, both vocalization frequencies are emitted in response to noxious stimuli. Thus, while rostral and caudal lesions may selectively block vocalization at a particular frequency (sonic vs. ultrasonic, respectively), there is no

reason to believe that either lesion alone should completely eliminate subjects' ability to respond.

However, these observations do not rule out the possibility that more sensitive measures of vocalization could reveal group differences. Indeed, during shock exposure, caudal lesions attenuated the magnitude of shock-induced vocalization. These were recorded using the same microphone employed during testing. Collapsed across the 3 shocks, the levels of vocalization for sham, rostral, and caudal groups were 88.0 (± 0.623), 89.6 (± 0.798), and 85.5 (± 0.529) dB, respectively. An ANOVA confirmed that the main effect of lesion was statistically significant, $\underline{F}$ (2,37) = 5.73, $\underline{p} < .01$. Further examination using a Duncan's multiple range analysis verified that rats in the caudal lesion condition vocalized less than rats in either the sham or rostral conditions. No other differences were significant. The fact that caudal-lesioned rats vocalized less during shock is somewhat troubling in that it allows for an alternative interpretation of my results: lesions might eliminate enhanced pain reactivity, not by destroying part of the neural circuitry responsible for this effect, but rather by reducing the aversiveness of the inducing agent and thus attenuating the *induction* of hyperalgesia. However, this account also predicts that the lesions should attenuate the induction of antinociception, but if anything, caudal lesions enhanced the antinociception response observed after shock. Moreover, such an interpretation cannot explain the elimination of hyperalgesia by rostral lesions, which had no impact on reactivity to shock.

Recently, we have begun to explore the role of other neural systems in hyperalgesia. In particular, we have looked at the impact of lesions of the amygdala and bed nucleus of the stria terminalis (BNST) on our effects -- a study motivated by

theories suggesting that fear (amygdala) and anxiety (BNST) may differentially affect hyperalgesia. Supporting this, we found that amygdala, but not BNST, lesions eliminated enhanced shock reactivity following previous exposure to shock (Crown, King, McLemore, Meagher, & Grau, 1998). Findings such as these, along with considerable neuroanatomical and behavioral evidence, have lead us to propose a neural model (see Figure 4) that might underlie shock-induced hyperalgesia and help to explain our behavioral data. From this model, it is important to note the excitatory projection extending from the dlPAG to the central nucleus of the amygdala, a projection that has often been overlooked or ignored in studies of fear conditioning and pain modulation. We believe that this connection is critical to our effect and is essential to the facilitation of fear conditioning following exposure to shock.

Such a model is attractive in that it makes clear predictions regarding hyperalgesia and fear conditioning, predictions that will need to be tested in order to confirm our inferences. For instance, because the model suggests that the dlPAG is not directly involved in fear conditioning but rather serves to enhance this conditioning under certain circumstances, one would not expect lesions of this region to disrupt conditioning that does not require prior exposure to shock (e.g., training with a more intense shock). Also, our model predicts that chemical activation of the dlPAG should serve as a substitute for the inducing shock and produce similar behavioral patterns. Together these studies should provide a building block for identifying the neuroanatomical and neurochemical systems that modulate pain reactivity and possibly lead to a better understanding of nociceptive processing in general. Our hope is that this understanding, in turn, will motivate future surgical and pharmacological research and lead to improvements in the treatment of pain.

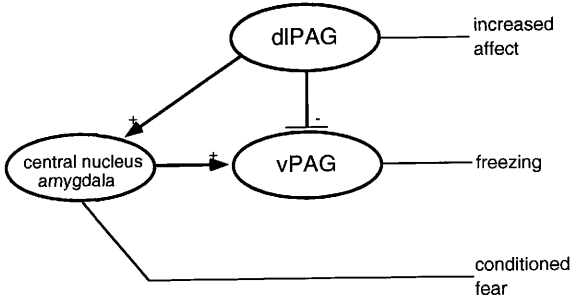

Figure 4. Proposed neural model of hyperalgesia and fear conditioning. The model includes the central nucleus of the amygdala, the dorsolateral periaqueductal gray (dlPAG), and the ventrolateral periaqueductal gray (vPAG) as well as their neural connections.

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